

# SCIENTIFIC COMPENDIUM: RESEARCH ON BRAIN SENSING



Scientific publications supporting the use of local field potentials (LFPs) as signals of interest in deep brain stimulation (DBS).

# INTRODUCTION

**This scientific compilation of published literature focuses on research questions that have helped to develop the field of brain sensing in Parkinson's disease.**

**This compilation is intended to provide a scientific overview on research characterizing brain signals recorded from patients. Since the majority of brain-sensing research to date has focused on Parkinson's disease, the Compendium focuses on providing scientific references to help understand the background of brain sensing in these patients. Literature was selected to provide examples of research that may be relevant to current use and implementation of commercial sensing features in the Medtronic Percept™ PC neurostimulator (CE Mark under review).**

## DISCLAIMERS

**This scientific compilation of published literature is provided for general educational purposes only and should not be considered the exclusive source for this type of information.**

While brain signals are becoming better characterized and understood, these articles should be appreciated as scientific research with several limitations:

- There is still much to learn regarding brain signals and their relationship to the normal brain, disease state, and therapy. The summarized articles support the science of brain signals and may be helpful tools for navigating the clinical use of brain sensing. However, interpretation of the data is limited due to short-term, in-clinic testing and small sample sizes in those with implanted neurostimulators.
- This document does not provide a full bibliography of all research in this space. Articles were selected as fair and balanced examples of "state of the art" for sensing research for Parkinson's disease. The articles address some common questions that have been and are being asked in brain sensing research.
- Some of the articles describe acute postoperative research investigating brain signals and their relationship to symptoms, treatments, or physical movements with externalized leads. These scientific findings may or may not be applicable to the utilization of sensing with chronically implanted systems; short-term, in-clinic LFP recording with externalized leads is not common clinical practice and is not endorsed by Medtronic.

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<p><b>1 What is a local field potential (LFP)?</b></p> <p>LFPs represent the summed electrical activity from local neuronal transmembrane currents around an electrode. Important factors that contribute to the LFP include the cellular and synaptic cellular architecture and the synchrony of the current sources.</p> <p>LFPs have been characterized into frequency bands (approximate range, Hz): delta (0-3), theta (4-7), alpha (8-12), beta (13-30), gamma (31-200) and high frequency (&gt; 200), although literature related to oscillatory activity in the basal ganglia broadly describes beta in the 8 to 30 Hz range. While changes in activity within each frequency band contribute to normal brain processing, persistent activity in the beta frequency range has been associated with the withdrawal of antiparkinsonian medication and the return of symptoms in patients with Parkinson’s disease. Therefore, persistent beta activity has been considered an “antikinetic” signal. The appearance of frequencies in a gamma range (60-90 Hz) in the basal ganglia may be related to the “vigor or effort” of a motor response and have been called “prokinetic.”</p>	6
<p><b>2 How do LFPs relate to the symptoms of Parkinson’s disease?</b></p> <p>Literature is fairly consistent in supporting an association between the presence of the beta band and the symptoms of bradykinesia and rigidity. Exaggerated beta band activity has been shown to decrease following antiparkinsonian medication and in a voltage-dependent manner with DBS. A reduction in persistent beta band activity has also been associated with improvements in UPDRS-III scores after DBS implant. Conversely, an increase in beta band has been observed with increased presence of bradykinesia. The presence of the beta band in patients with tremor dominant symptoms has been less clear. Other frequency bands, including activity around the tremor frequency (e.g. 4-5 Hz) and high frequency activity (e.g. 35-55 Hz), have had some association with rest tremor. Beta energy is lower during movement such as walking.</p>	11

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<p><b>3 The persistence of LFPs over time in patients with Parkinson’s disease.</b></p> <p>Several studies have investigated the persistence of beta band LFPs over time in patients with Parkinson’s disease. While LFP magnitude and peak frequency often differ between patients while at rest, beta activity in individual study patients has been generally consistent when recorded 1 year or more after lead implant. However, variability has also been described, with beta LFPs decreasing or increasing in magnitude from baseline measurements.</p>	17
<p><b>4 Selected sensing research with implanted Activa™ PC+S neurostimulators.</b></p> <p>Research has been conducted for several years using implanted neurostimulators with sensing capabilities. This section provides examples of research performed to investigate and better understand LFPs as they relate to Parkinson’s disease, medication, DBS therapy, and movement in patients implanted with a device with sensing capabilities. These publications focus on research questions conducting in-clinic assessment of LFPs.</p>	20
<p><b>5 Literature on Additional Topics</b></p> <p>There are many potential topics and questions related to sensing LFPs. In addition to the topics listed above, citations for several frequently discussed topics are provided here.</p> <ul style="list-style-type: none"> <li>▪ Localization of LFPs in the STN</li> <li>▪ Localization of LFPs in the GPi</li> <li>▪ LFPs and dyskinesias</li> </ul>	25

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# WHAT IS A LOCAL FIELD POTENTIAL (LFP)?

## ARTICLE

**Brown and Williams. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol. 2005;116( 11):2510-9.**

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=16029963>

## SUMMARY

The article provides an introduction on LFP activity in the basal ganglia and describes well-characterized LFP oscillations in the 8 to 30 Hz range. Patients with Parkinson's disease tend to have 8 to 30 Hz activity in the subthalamic nucleus (STN) and internal globus pallidus (GPI) particularly when off dopaminergic medication. Therefore, this "frequency band" may be related to movement, showing increased power in akinetic states and decreased power prior to voluntary movement.

## ARTICLE

**Rosa M., Marceglia S., Barbieri S., Priori A. Local Field Potential and Deep Brain Stimulation (DBS). In: Jaeger D., Jung R. (eds) Encyclopedia of Computational Neuroscience. Springer, New York, NY; 2014.**

Open Access: [https://doi.org/10.1007/978-1-4614-7320-6\\_547-1](https://doi.org/10.1007/978-1-4614-7320-6_547-1)

## SUMMARY

The chapter provides a summary of literature reporting LFP sensing in patients with Parkinson's disease at rest and during movement, with medication ON and OFF, and immediately after or during DBS. Several tables summarize whether specific frequency bands tend to increase or decrease under these conditions. For example, low beta (13-20 Hz) and high beta (21-35 Hz) signals recorded in the STN tend to be higher at rest with medication OFF and decrease in magnitude with medication ON and during movement. With DBS, beta activity tended to decrease, while low frequency activity tended to increase. However, the authors also noted that the results varied between the studies. Research reporting on findings from patients with essential tremor is also summarized.

**Notes:** Differences in recording techniques (i.e. immediately after DBS versus during DBS) and patient characteristics (i.e. those with high global beta versus a range of beta amplitudes) were discussed as factors that may have influenced study outcomes.

## ARTICLE

**Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol. 2013;26(6):662-70.**

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24150222>

## SUMMARY

The article reviews LFP activity in the alpha, beta, and gamma frequency bands within the corticobasal ganglia circuit of patients with Parkinson's disease. The 15 to 35 Hz beta band has been associated with bradykinesia and rigidity, but has not been associated with the severity of Parkinsonian tremor. Frequencies in a gamma range (60 to 90 Hz) have been recorded in the internal globus pallidus, subthalamic nucleus, and cortical areas and may be related to the "vigor or effort" of a motor response, i.e. prokinetic. Phase amplitude coupling (PAC) is described as the ability of the phase of a low-frequency signal to drive the amplitude of a higher oscillation. PAC may play a role in brain network communication and may be altered in disease states.

**Notes:** The authors discussed that it may be tempting to classify oscillatory activity in Parkinson's disease as purely akinetic (beta band) or prokinetic (gamma band). However, this simplistic view does not fully capture or describe the role of LFPs in the brain. These oscillations are important for normal brain function and have many cross-frequency relationships.

## ARTICLE

**Eusebio A, Brown P. Synchronisation in the beta frequency-band--the bad boy of parkinsonism or an innocent bystander? Exp Neurol. 2009;217(1):1-3.**

Open Access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697315/>

## SUMMARY

This article cautions against the assumption that beta oscillations have a mechanistic role in the symptoms of Parkinson's disease. Commentary and evidence "for and against a role for excessive beta synchrony in mediating the parkinsonian phenotype" are described. The authors conclude that beta synchrony appears to be a good signal of interest associated with the akinetic-rigid state in patients and animal models. However, the quantitative importance of beta synchrony and the mechanism by which it might disrupt motor processing is still unknown.

## ARTICLE

Buzsáki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes. *Nat Rev Neurosci*. 2012 18;13(6):407-20.

Open Access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4907333/>

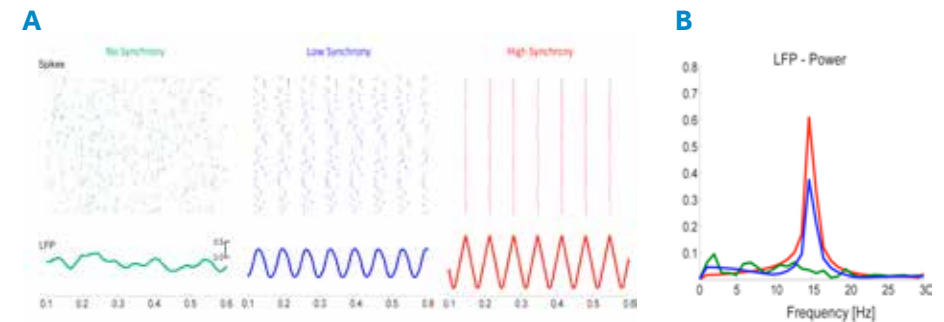
## SUMMARY

This article is a scientific review describing the origin and detection of extracellular neuronal activity, including LFPs. Transmembrane currents (including action potentials and after hyperpolarizations) lead to intracellular and extracellular voltage deflections. The characteristics of the intracranial LFP will depend on several factors including: the neural current sources, properties of the brain tissue, electrode distance from the sources, and the temporal coordination (synchrony) of the current sources. Electroencephalograms (EEG) and electrocortograms (ECoGs) are examples of recording “macroscopic” extracellular activity from superficial layers of the cortex, while microelectrodes within the brain can record “microscopic” single-neuron spiking activity. LFPs provide information between these two types of measurements.

## OTHER ARTICLES OF INTEREST

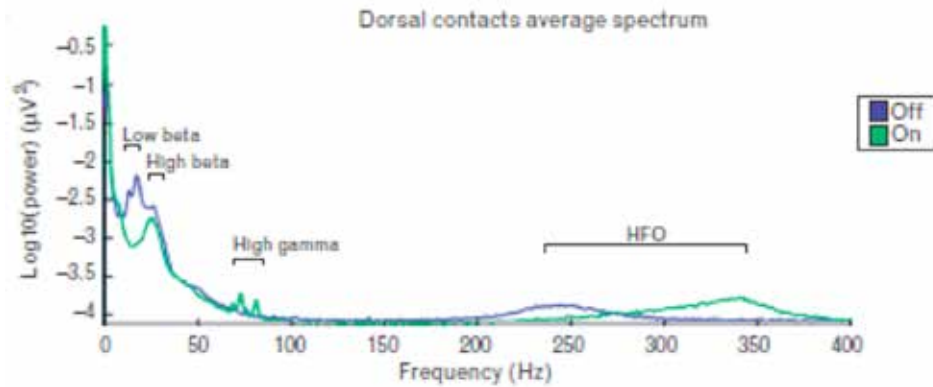
- Thompson JA, Lanctin D, Ince NF, Abosch A. Clinical implications of local field potentials for understanding and treating movement disorders. *Stereotact Funct Neurosurg*. 2014;92(4):251-63.
- Brittain JS, Brown P. Oscillations and the basal ganglia: motor control and beyond. *Neuroimage*. 2014;85 Pt 2:637-47.

## Figures 1-2. Examples of LFP Power and LFPs with Medication OFF and ON



**Figure 1.** Schematic showing the synchronization of neuronal spiking behavior into oscillatory behavior (A), representing frequency bands of different power strengths (B). Synchronization may promote interaction between neuronal populations. Modified from Figure 6 in: Hanslmayr S., Staudig T., Fellner M.-C. Oscillatory power decreases and long-term memory: The information via desynchronization hypothesis. *Front Hum Neurosci*. 2012;6:74. Use is covered under a Creative Commons license: <https://creativecommons.org/licenses/by/4.0/>.

# HOW DO LFPS RELATE TO THE SYMPTOMS OF PARKINSON'S DISEASE?



**Figure 2.** Frequency spectrum during rest in a cohort of patients (n = 14) with PD in medication ON and medication OFF states. With medication ON, there is a reduction in low frequency beta power, but not high beta power. Peaks can also be seen in the theta/alpha, gamma, and high frequency (250–350 Hz) bands. The small change in gamma was attributable to 3 out of 15 subjects. Figure from: López-Azcárate J, Tainta M, Rodríguez-Oroz MC, et al. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. *J Neurosci.* 2010;30(19):6667–77. Used with permission from the Journal of Neuroscience.

## ARTICLE

Kühn AA, Kupsch A, Schneider GH, Brown P. Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur J Neurosci.* 2006;23(7):1956–60.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=16623853>

## SUMMARY

STN LFPs were recorded from 9 patients an average of 5.7 days after bilateral DBS lead implantation. Recordings from externalized leads started with the patients at rest with medication OFF and continued for about 1 hour after taking antiparkinsonian medication. Power changes in the 8 to 35 Hz (alpha/beta) and 60 to 90 Hz (gamma) range were analyzed for their correlation to UPDRS hemibody scores (contralateral to the recording site). The majority of hemispheres (11/17 sides) showed peaks in the 14 to 35 Hz range (beta); fewer sides (6/17) had peaks between 8 and 13 Hz (alpha). Individual LFP peaks were reduced by medication, and the reduction positively correlated with the improvement in UPDRS score. There was a positive correlation with akinesia-rigidity, but not with tremor. A subgroup of 7 sides showed a distinct gamma peak with medication ON, and a trend for a negative correlation with UPDRS improvement. However, reduction in 8 to 35 Hz frequency positively correlated with motor improvement in this subgroup.

**Limitations and notes:** Recordings were conducted in the immediate postoperative period. One patient did not have a distinct peak in the 8–35 Hz range and was excluded from the analysis.

## ARTICLE

**Quinn EJ, Blumenfeld Z, Velisar A, et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. *Mov Disord.* 2015;30(13):1750-8.**

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/26360123>

## SUMMARY

Patients (n = 14) classified as being tremor dominant (n = 7) or akinetic rigid (n = 7) performed ordered movement sequences consisting of sitting, standing, lying down, and forward walking. In addition, stimulation at 140 Hz with randomized amplitudes of 0 V, 1 V, and 3 V (or maximum tolerated) was presented to the patient while seated. Recordings were performed with an implanted neurostimulator under medication OFF and DBS OFF prior to initial programming or up to 3 months after implant. Data included STN LFPs, limb angular velocity, surface electromyography (EMG), and video of movement. Power spectral density traces (PSDs) were used to compare beta band power under different conditions. PSDs were similar between lying down, sitting, and standing. When forward walking, akinetic rigid subjects tended to have decreased beta band power compared to the other positions. Beta band power decreased in a voltage-dependent manner with DBS.

**Limitations and notes:** In some cases, alternate stimulation electrodes were chosen to avoid low-frequency electrocardiogram artifact in the recording. The authors commented that the small sample size prevented phenotype comparisons during the different movement tasks.

## ARTICLE

**Trager MH, Koop MM, Velisar A, et al. Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease. *NeurobiolDis.* 2016;96:22-30.**

PubMed Link: <https://www.ncbi.nlm.nih.gov/pubmed/27553876>

## SUMMARY

STN LFPs were analyzed via an implanted neurostimulator capable of sensing in subjects at 6 months (17 subjects) and 12 months (10 subjects) postsurgery, after withdrawal of chronic DBS. Subjects were classified as akinetic rigid (n = 8) or tremor dominant (n = 9). Beta power was recorded at both time points, and beta power after immediate withdrawal of DBS was similar to beta recorded 60 min later. Compared to baseline measurements,

the UPDRS scores (with DBS OFF) were improved at 6- and 12-months; beta band power was also significantly lower compared to baseline with DBS OFF. There was a positive correlation between the improvement in UPDRS score and reduction in beta power in the akinetic rigid cohort. The UPDRS III score and beta power were inversely correlated in the patients with tremor dominance. Beta power gradually increased in two unstimulated STNs after 24 months.

**Limitations and notes:** The analysis was limited by only 10 subjects providing data at the 12-month follow-up and the UPDRS scores were not conducted by an evaluator who was blinded to the patient condition. Electrocardiography artifacts were mentioned as providing possible interference with the LFP recording. Beta power varied across subjects.

## ARTICLE

**Neumann WJ, Staub-Bartelt F, Horn A, et al. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. *Clin Neurophysiol.* 2017;128(11):2286-2291.**

Open Access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5779610/>

## SUMMARY

A total of 15 patients with an implanted neurostimulator capable of sensing were recruited; STN LFPs were analyzed in 12 patients in an ON and OFF levodopa state, with DBS OFF, at 3- and 8-months postsurgery. Beta band (13-35 Hz) peaks could be identified in all hemispheres and data were analyzed by aligning the peak power spectra centers (rather than averaging the power spectra). Peak beta amplitude and UPDRS III scores were significantly reduced with medication ON at all time points. The authors showed that the association between beta amplitude and motor outcomes "remain consistent over time, even after successful long-term DBS."

**Limitations and notes:** Three patients were excluded from the analysis: 2 refused to withdraw from medication; 1 did not complete the 8-month follow-up. The duration of LFP recording was limited to approximately 1 minute for each bilateral contact pair and peak beta amplitudes were "relatively small." Cardioelectric pulse artifacts were seen in the majority of 0-1 contact pairs. UPDRS scores were conducted by an evaluator that was not blinded to the patient information.



## OTHER ARTICLES OF INTEREST: LFPs AND SYMPTOMS OF PARKINSON'S DISEASE

- Neumann WJ, Degen K, Schneider GH, et al. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Mov Disord.* 2016;31(11):1748-1751.
- Shreve LA, Velisar A, Malekmohammadi M, et al. Subthalamic oscillations and phase amplitude coupling are greater in the more affected hemisphere in Parkinson's disease. *Clin Neurophysiol.* 2017;128(1):128-137.
- Kuhn AA, Williams D, Kupsch A, et al. Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain.* 2004;127(Pt 4):735-46.
- Little S, Pogosyan A, Kuhn AA, Brown P.  $\beta$  band stability over time correlates with Parkinsonian rigidity and bradykinesia. *Exp Neurol.* 2012;236(2):383-8.
- van Wijk BC, Beudel M, Jha A, et al. Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. *Clin Neurophysiol.* 2016;127(4):2010-9.
- Kuhn, Kempf F, Brücke C, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J Neurosci.* 2008;28(24):6165-73.

## OTHER ARTICLES OF INTEREST: LFPs AND ANTIPARKINSONIAN MEDICATION

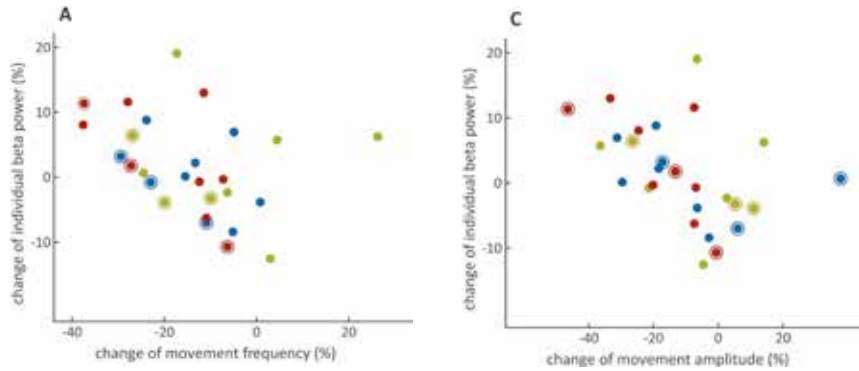
- Neumann WJ, Degen K, Schneider GH, et al. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Mov Disord.* 2016;31(11):1748-1751.
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## OTHER ARTICLES OF INTEREST: LFPs AND DBS

- Neumann WJ, Staub F, Horn A, et al. Deep Brain Recordings Using an Implanted Pulse Generator in Parkinson's Disease. 2016. 19(1): p. 20-4.
- Eusebio A, Thevathasan W, Doyle Gaynor L, et al. Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. *Neurol Neurosurg Psychiatry.* 2011;82(5):569-73.
- Giannicola G, Marceglia S, Rossi L, et al. The effects of levodopa and ongoing deep brain stimulation on subthalamic beta oscillations in Parkinson's disease. *Exp Neurol.* 2010;226(1):120-7.
- Rosa M, Giannicola G, Servello D, et al. Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. *Neurosignals.* 2011;19(3):151-62.



**Figure 3. Example of LFP Power with DBS OFF and ON and relationship to PD symptoms**



**Figure 3.** Changes in beta power were associated with decrements in the frequency (A) and amplitude (C) of a repetitive movement. Increases in beta power were associated with a decrease in movement frequency or amplitude, indicating increased beta with bradykinesia. Circles indicate data for each individual patient undergoing 3 blocks of movement testing (red = block 1; blue = block 2; khaki = block 3). Steiner LA, Neumann WJ, Staub-Bartelt F, et al. Subthalamic beta dynamics mirror Parkinsonian bradykinesia months after neurostimulator implantation. *Mov Disord.* 2017;32(8):1183-1190; publisher, Wiley. Available at <https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.27068>. This article and its use herein is covered under a HYPERLINK "<https://creativecommons.org/licenses/by/4.0/>" Creative Commons Attribution License (CC BY). Figure 4 of the article was modified to show Panels A and C.

## PERSISTENCE OF LFP SIGNALS OVER TIME IN PATIENTS WITH PARKINSON'S DISEASE

### ARTICLE

Neumann WJ, Staub-Bartelt F, Horn A, et al. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. *Clin Neurophysiol.* 2017;128(11):2286-2291.

Open Access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5779610/>

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**Limitations and notes:** Three patients were excluded from the analysis: 2 refused to withdraw from medication; 1 did not complete the 8-month follow-up. The duration of LFP recording was limited to approximately 1 minute for each bilateral contact pair and peak beta amplitudes were "relatively small." Cardioelectric pulse artifacts were seen in the majority of 0-1 contact pairs. UPDRS scores were not conducted by a blinded evaluator.

### ARTICLE

Hanrahan SJ, Nedrud JJ, Davidson BS, et al. Long-Term Task- and Dopamine-Dependent Dynamics of Subthalamic Local Field Potentials in Parkinson's Disease. *Brain Sci.* 2016;6(4):E57.

Open Access: <http://dx.doi.org/10.3390/brainsci6040057>

### SUMMARY

Bilateral STN LFP recordings were collected over a period of 12 months in 7 subjects with an implanted neurostimulator capable of sensing. Recordings were conducted with medication ON at all time points except during the intraoperative and 6-month

recordings; DBS was off during these recordings. While the beta band showed much intersubject variability, the authors "observed consistent STN-LFP activity across recording systems and over a one-year period for each subject." Beta power from the therapeutic contacts did not vary with medication state while the subject was at rest, but could be desynchronized with a behavioral task. Gamma band synchronization was only seen in the medication ON state, but was "inconsistently observed."

**Limitations and notes:** Medication ON and medication OFF states were not collected at each time point; data was compared across time points which may have influenced the results. The authors commented that variation between subjects "may stem from differences in DBS lead location within the STN, the level of patient's PD progression, prescribed medication, predominant PD symptoms and unknown factors."

## ARTICLE

**Trager MH, Koop MM, Velisar A, et al. Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease. NeurobiolDis, 2016;96:22-30.**

PubMed Link: <https://www.ncbi.nlm.nih.gov/pubmed/27553876>

## SUMMARY

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**Limitations and notes:** The analysis was limited by only 10 subjects providing data at the 12-month follow-up and the UPDRS scores were not conducted by a blinded evaluator. Electrocardiography artifacts were mentioned as providing possible interference with the LFP recording. Beta power varied across subjects.

## ARTICLE

**Giannicola G, Rosa M, Servello D, et al. Subthalamic local field potentials after seven-year deep brain stimulation in Parkinson's disease. Exp Neurol. 2012;237(2):312-7.**

PubMed Link: <https://www.ncbi.nlm.nih.gov/pubmed/22735488>

## SUMMARY

STN LFPs were studied in patients (n = 11) at 7 years after DBS implant (hyperchronic group) and in patients (n = 16) at 3 days after lead implantation (acute group). In both groups of patients, LFPs were collected with external equipment (data from the hyperchronic group was collected during neurostimulator replacement surgery). Without DBS, no differences were detected between the two groups in low frequency (LF) or beta oscillations. With DBS, the population analysis showed an increase in LF power and no change in other power frequencies. In the nuclei with strong beta at baseline (56% of samples in acute; 61% of samples in hyperchronic), DBS decreased beta power in both subgroups. The authors concluded that the LFP pattern recorded after DBS lead placement remains stable out to 7-years postsurgery.

**Limitations and notes:** Different patients were analyzed in the acute and chronic settings, so longitudinal comparisons could not be made. LFPs were recorded with external equipment for durations lasting between 30 and 60 minutes.

## ARTICLE

**Abosch A, Lanctin D, Onaran I, et al. Long-term recordings of local field potentials from implanted deep brain stimulation electrodes. Neurosurgery. 2012;71(4):804-14.**

PubMed Link: <https://www.ncbi.nlm.nih.gov/pubmed/?term=22791039>

## SUMMARY

STN LFPs were recorded in groups of patients at different time points: during surgery (n = 9 subjects), 3 weeks after lead placement (n = 9), and a median of 3.5 years after surgery, during neurostimulator replacement (n = 7). Two patients provided data at all 3 time points. Recordings were conducted with medication OFF. Beta band amplitude was similar at initial lead implant and 3-weeks postsurgery. Beta was measurable years after initial lead implant, although the amplitude was significantly lower than the earlier time points.

**Limitations and notes:** Different patients were analyzed in the acute and chronic settings; except for 2 patients, longitudinal comparisons could not be made. In most subjects, a decrease in beta amplitude was associated with movement; however, movement caused amplitude increases in a subset of patients. LFPs were recorded with external equipment for a limited amount of time.

# SELECTED SENSING RESEARCH WITH IMPLANTED ACTIVA™ PC+S NEUROSTIMULATORS

## ARTICLE

Quinn EJ, Blumenfeld Z, Velisar A, et al. **Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. *Mov Disord.* 2015;30(13):1750-8.**

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/26360123>

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Patients (n = 14) classified as being tremor dominant (n = 7) or akinetic rigid (n = 7) performed ordered movement sequences consisting of sitting, standing, lying down, and forward walking. In addition, stimulation of 140 Hz with randomized amplitudes of 0 V, 1 V, and 3 V (or maximum tolerated) was presented to the patient while seated. Recordings were performed with an implanted neurostimulator under medication OFF and DBS OFF prior to initial programming or up to 3 months after implant. Data included STN LFPs, limb angular velocity, surface electromyography (EMG), and video of movement. Power spectral density traces (PSDs) were used to compare beta band power under different conditions. PSDs were similar between lying down, sitting, and standing. When forward walking, akinetic rigid subjects tended to have decreased beta band power compared to the other positions. Beta band power decreased in a voltage-dependent manner with DBS.

**Limitations and notes:** In some cases, alternate stimulation electrodes were chosen to avoid low-frequency electrocardiogram artifact in the recording. The authors commented that the small sample size prevented phenotype comparisons during the different movement tasks.

## ARTICLE

Neumann WJ, Staub F, Horn A, et al. **Deep Brain Recordings Using an Implanted Pulse Generator in Parkinson's Disease. *Neuromodulation.* 2016;19(1):20-24.**

Open Access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4881811/>

## SUMMARY

The study reported on 8 patients implanted with bilateral STN. Recordings were conducted with an implanted neurostimulator in a medication OFF state several days after DBS surgery. Sessions began with DBS turned off, followed by 15 minutes of stimulation ON before continuing the recording. Fifteen contact pairs provided data (data from one contact pair was contaminated by cardiac pulse artifacts and was excluded). Data with DBS ON was compared with DBS OFF across alpha (7-12 Hz) and beta (13-30 Hz) frequency bands. DBS on significantly reduced beta band power; however, no change occurred in the alpha band.

**Limitations and notes:** A distinct beta band was not present in the averaged group data, and could only be recovered by aligning the individual peaks before averaging. Distinct peaks in beta activity could be recorded in 80% of leads (12 of 15); the authors commented that technical issues or stun effects may have impacted recording capabilities.

## ARTICLE

Trager MH, Koop MM, Velisar A, et al. **Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease. *NeurobiolDis.* 2016;96:22-30.**

PubMed Link: <https://www.ncbi.nlm.nih.gov/pubmed/27553876>

## SUMMARY

STN LFPs were analyzed via an implanted neurostimulator capable of sensing in subjects at 6 months (17 subjects) and 12 months (10 subjects) postsurgery, after withdrawal of chronic DBS. Subjects were classified as akinetic rigid (n = 8) or tremor dominant (n = 9). Beta power was recorded at both time points, and beta power after immediate withdrawal of DBS was similar to beta recorded 60 min later. Compared to baseline measurements, the UPDRS scores (with DBS OFF) were improved at 6- and 12-months; beta band power was also significantly lower compared to baseline with DBS OFF. There was a positive correlation between the improvement in UPDRS score and reduction in beta power in the akinetic rigid cohort. The UPDRS III score and beta power were inversely correlated in the patients with tremor dominance. Beta power gradually increased in two unstimulated STNs after 24 months.

**Limitations and notes:** The analysis was limited by only 10 subjects providing data at the 12-month follow-up and the UPDRS scores were not conducted by a blinded evaluator. Electrocardiography artifacts were mentioned as providing possible interference with the LFP recording. Beta power varied across subjects.

## ARTICLE

**Hanrahan SJ, Nedrud JJ, Davidson BS, et al. Long-Term Task- and Dopamine-Dependent Dynamics of Subthalamic Local Field Potentials in Parkinson's Disease. *Brain Sci.* 2016;6(4):E57.**

Open Access: <http://dx.doi.org/10.3390/brainsci6040057>

## SUMMARY

Bilateral STN LFP recordings were collected over a period of 12 months in 7 subjects with an implanted neurostimulator capable of sensing. Recordings were conducted with medication ON at all time points except during the intraoperative and 6-month recordings; DBS was off during the recordings. While the beta band showed much intersubject variability, the authors "observed consistent STN-LFP activity across recording systems and over a one-year period for each subject." Beta power from the therapeutic contacts did not vary with medication state while the subject was at rest, but could be desynchronized with a behavioral task. Gamma band synchronization was only seen in the medication ON state, but was "inconsistently observed."

**Limitations and notes:** Medication ON and medication OFF states were not collected at each time point; data was compared across time points which may have influenced the results. The authors commented that variation between subjects "may stem from differences in DBS lead location within the STN, the level of patient's PD progression, prescribed medication, predominant PD symptoms and unknown factors."

## ARTICLE

**Canessa A, Pozzi NG, Arnulfo G, et al. Striatal Dopaminergic Innervation Regulates Subthalamic Beta-Oscillations and Cortical-Subcortical Coupling during Movements: Preliminary Evidence in Subjects with Parkinson's Disease. *Front Hum Neurosci.* 2016;10:611.**

Open Access: <http://dx.doi.org/10.3389/fnhum.2016.00611>

## SUMMARY

STN LFP activity recorded with an implanted neurostimulator and cortical electroencephalography (EEG) signals were investigated in patients with Parkinson's disease. A total of 7 subjects were evaluated 4 months postsurgery in a medication OFF state. Cortical EEG and STN LFPs were measured while the subject performed motor tasks. A subset of patients were included in a single-photon computed tomography (SPECT) scan using [<sup>123</sup>I]N- $\omega$ -fluoropropyl-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-odophenyl) nortropane (FP-CIT) to investigate dopamine innervation in the striatum. The SPECT

imaging classified STNs according to a lower/higher striatal-specific binding ratio. The greatest suppression of beta activity during movement occurred in the most dopamine-depleted hemisphere. The authors hypothesized that "movement-related beta-modulation is dependent on striatal dopaminergic innervation." Cortical-subcortical and interhemispheric subcortical coherencies were also analyzed.

**Limitations and notes:** The study is limited by its small sample size, which was reduced from an initial 7 patients since 3 patients were unable to complete the movement task. Their data were excluded from the analysis.

## ARTICLE

**Neumann WJ, Staub-Bartelt F, Horn A, et al. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. *Clin Neurophysiol.* 2017;128(11):2286-2291.**

Open Access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5779610/>

## SUMMARY

A total of 15 patients with an implanted neurostimulator capable of sensing were recruited; STN LFPs were analyzed in 12 patients in an ON and OFF levodopa state, with DBS OFF, at 3- and 8-months postsurgery. Beta band (13-35 Hz) peaks could be identified in all hemispheres and data was analyzed by aligning the peak power spectra centers (rather than averaging the power spectra). Peak beta amplitude and UPDRS III scores were significantly reduced with medication at all time points. The authors showed that the association between beta amplitude and motor outcomes "remain consistent over time, even after successful long-term DBS."

**Limitations and notes:** Three patients were excluded from the analysis: 2 refused to withdraw from medication; 1 did not complete the 8-month follow-up. The duration of LFP recording was limited to approximately 1 minute for each bilateral contact pair and peak beta amplitudes were "relatively small." Cardioelectric pulse artifacts were seen in the majority of 0-1 contact pairs. UPDRS scores were conducted by an evaluator that was blinded to patient information.

## ARTICLE

**Steiner LA, Neumann WJ, Staub-Bartelt F, et al. Subthalamic beta dynamics mirror Parkinsonian bradykinesia months after neurostimulator implantation. *Mov Disord.* 2017;32(8):1183-1190.**

Open Access: <http://dx.doi.org/10.1002/mds.27068>

## SUMMARY

The study focused on the relationship between beta band activity and bradykinesia associated with structured repetitive pronation-supination movements with medication OFF and DBS turned off. Recordings from an implanted neurostimulator were obtained in 9 patients with either 8 months (n = 6) or 3 months (n = 3) of bilateral STN DBS. Beta power was suppressed during the movements, but began to gradually increase over time as the frequency and amplitude of the movement decreased (i.e. with increasing bradykinesia).

**Limitations and notes:** A total of 15 patients were enrolled in the study; however, beta activity could not be detected in 3 patients, which the authors speculate could be due to targeting, technical issues, or device-related issues. In addition, data could not be collected from 2 patients due to technical issues and severe tremor in another patient interfered with the movement task.

## ARTICLE

**Blumenfeld Z, Koop MM, Prieto TE, et al. Sixty-hertz stimulation improves bradykinesia and amplifies subthalamic low-frequency oscillations. *Mov Disord.* 2017;32(1):80-88.**

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=27859579>

## SUMMARY

STN LFPs were recorded with an implantable neurostimulator while patients (n = 9) performed an upper extremity repetitive wrist flexion-extension task at least 1 month after implantation. The baseline condition consisted of both DBS and medication OFF. Subsequently, stimulation was randomized to 60 Hz or 140 Hz (amplitude, 2 V or 3 V), and in some cases 20 Hz. Both 140 Hz and 60 Hz improved the angular velocity and frequency of movement. Only 140 Hz broadly attenuated beta-band power compared with baseline. 60 Hz DBS amplified alpha/low beta power, but attenuated high beta oscillations. Since 60 Hz decreased limb bradykinesia but did not attenuate all oscillatory activity, the authors suggested that suppression of all beta band oscillations may not be required for attenuation of bradykinesia.

**Limitations and notes:** Study limitations discussed by the authors included the short-term (3 min) stimulation and recording, differing total energy requirements between frequencies, and the small sample size.

## LITERATURE ON ADDITIONAL TOPICS

### OTHER ARTICLES OF INTEREST: LOCATION OF LFPs IN THE STN

Pogosyan A, Yoshida F, Chen CC, et al. Parkinsonian impairment correlates with spatially extensive subthalamic oscillatory synchronization. *Neuroscience.* 2010;171(1):245-57.

Horn A, Neumann W, Degen K, et al. Toward an electrophysiological “sweet spot” for deep brain stimulation in the subthalamic nucleus. *Hum Brain Mapp.* 2017;38(7):3377-3390.

van Wijk BCM, Pogosyan A, Hariz MI, et al. Localization of beta and high-frequency oscillations within the subthalamic nucleus region. *Neuroimage Clin.* 2017;16:175-183.

### OTHER ARTICLES OF INTEREST: SENSING OF LFPs IN THE GPI OF PATIENTS WITH PARKINSON'S DISEASE

Malekmohammadi M, Shahriari Y, AuYong N. et al. Pallidal stimulation in Parkinson disease differentially modulates local and network  $\beta$  activity. *J Neural Eng.* 2018;15(5):056016.

Wang DD, de Hemptinne C, Miocinovic S, et al. Pallidal Deep-Brain Stimulation Disrupts Pallidal Beta Oscillations and Coherence with Primary Motor Cortex in Parkinson's Disease. *J Neurosci.* 2018;38(19):4556-4568.

AuYong N, Malekmohammadi M, Ricks-Oddie J, et al. Movement-Modulation of Local Power and Phase Amplitude Coupling in Bilateral Globus Pallidus Interna in Parkinson Disease. *Front Hum Neurosci.* 2018;12:270.

### OTHER ARTICLES OF INTEREST: LFPs AND DYSKINESIAS

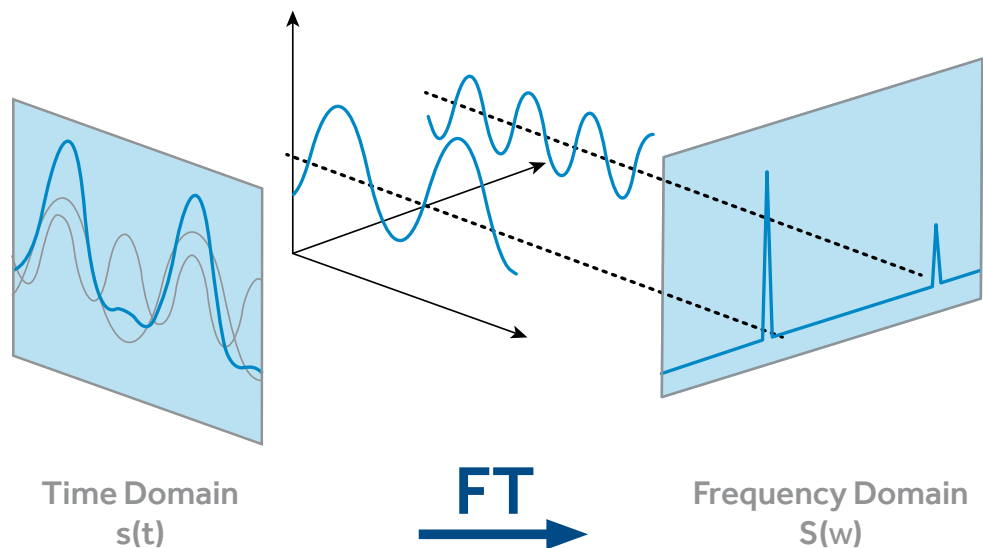
Alonso-Frech F, Zamarbide I, Alegre M, et al. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain.* 2006;129(Pt 7):1748-57.

Alegre M, López-Azcárate J, Alonso-Frech F, et al. Subthalamic activity during diphasic dyskinesias in Parkinson's disease. *Mov Disord.* 2012;27(9):1178-81.

# GLOSSARY

**Coherence** — An assessment of the association between activity recorded at two different sensors.<sup>1</sup>

**Fourier transform** — a method of “comparing” the data  $x$  to sinusoids oscillating at difference frequencies  $f_j$ . When the data and sinusoids “match,” the power at frequency  $f_j$  is large, whereas when the data and sinusoids do not match, the power at frequency  $f_j$  is small.<sup>1</sup>



**Oscillations** — rhythmic repetitive patterns of neural activity in the nervous system that can be recorded as extracellular LFPs.<sup>3</sup>

**Phase Amplitude Coupling (PAC)** — the ability of the phase of a low-frequency signal to drive the amplitude of a higher oscillation.<sup>2</sup>

**Power Spectrum** — the magnitude squared of the Fourier transform of the data. The power spectrum indicates the amplitude of rhythmic activity in the data as a function of frequency.<sup>1</sup>

1. Kramer MA. An Introduction to Field Analysis Techniques: The Power Spectrum and Coherence. White Paper. Kramer 2013. Accessed on-line 22 July 2019.
2. Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. *Curr Opin Neurol.* 2013;26(6):662-70.
3. Thompson JA, Lanctin D, Ince NF, Abosch A. Clinical implications of local field potentials for understanding and treating movement disorders. *Stereotact Funct Neurosurg.* 2014;92(4):251-63.

Common Acronyms	
PD	Parkinson's disease
STN	subthalamic nucleus
GPI	internal globus pallidus
LFP	local field potential
UPDRS	Unified Parkinson's Disease Rating Scale
PC+S	Primary Cell + Sensing

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